Efficient synthesis of functionalized 2-pyridones by ytterbium chloride catalyzed tandem condensation

WANG QianNan, YAO ZhiGang, XU Fan* & SHEN Qi*

Key Laboratory of Organic Synthesis, College of Chemistry, Chemical Engineering and Materials Science, Soochow University, Suzhou 215123, China

Received March 15, 2011; accepted May 31, 2011; published online February 21, 2012

An efficient method was developed for the synthesis of arylidene heterobicyclic 3-cyano-2-pyridones via ytterbium chloride catalyzed tandem condensation of aromatic aldehydes, cyclic ketones, and cyanoacetamide. The conditions and scope of the reaction were investigated and a reaction mechanism was proposed.

pyridone, ytterbium chloride, tandem reaction, catalysis, synthesis

Citation: Wang Q N, Yao Z G, Xu F, et al. Efficient synthesis of functionalized 2-pyridones by ytterbium chloride catalyzed tandem condensation. *Chin Sci Bull*, 2012, 57: 1612–1615, doi: 10.1007/s11434-011-4744-0

Tandem reactions are powerful methods for the synthesis of structurally complex compounds from simple substrates. Among the strategies used for the construction of biologically active molecules, tandem reactions for the design and synthesis of drug-like compounds are of particular interest to organic synthetic chemists. The 2-pyridone skeleton is an important substructure found in many natural or synthetic biologically active materials, and its derivatives have been applied in various pharmaceutical and biochemical fields. It is of great interest that specifically functionalized 2-pyridones may possess specific biological properties. For example, milrinone [1] (Scheme 1, **A**), which has a 3-cyano-2-pyridone core, is an effective cardiotonic agent. More recently, antitumor screening data showed that some fused 3-cyano-2-pyridones with an arylidene moiety [2] (Scheme 1, **B**) are potential antitumor agents. These findings indicate that efficient methods need to be developed for the synthesis of these 3-cyano-2-pyridones. According to the rather limited literature in this area, arylidene heterobicyclic 3-cyano-2-pyridones were synthesized in the presence of a base in a stepwise manner, with the necessary intermediates such as α,α' -bis(arylidene)cycloalkanones or

Scheme 1

2-cyano-3-phenylacrylates prepared and isolated in advance [2–7].

Lanthanide reagents have been increasingly applied and widely studied in organic synthesis in recent years [8–11]. Most of the lanthanides are nontoxic and relatively abundant in nature. The successful development of many useful reactions efficiently catalyzed by lanthanide compounds can be attributed to the unique features of lanthanide centers, such as their high electrophilicity, variable metal ion radius and tunable coordination patterns. Prompted by our previous studies on lanthanide halide-catalyzed synthesis of biologically relevant heterocyclic compounds [12–16], we investigated the effectiveness of lanthanide chlorides as catalysts

*Corresponding authors (email: xufan@suda.edu.cn; qshen@suda.edu.cn)

for the tandem preparation of arylidene heterobicyclic 3-cyano-2-pyridones. This type of synthesis is very important and attractive from the viewpoints of operational simplicity and assembly efficiency. Herein, we report our preliminary results from this investigation.

An initial trial was conducted with a three-component condensation of cyclopentanone **1a**, benzaldehyde **2a** and cyanoacetamide **3** (Scheme 2) in the presence of a catalytic amount of ytterbium chloride (YbCl_3), which is a readily available and economical lanthanide Lewis acid. To our surprise, 7-benzylidene-3-cyano-4-phenyl-3,4,6,7-tetrahydro-1*H*-cyclopenta[*b*]pyridin-2(5*H*)-one **4a** was obtained rather than the expected 7-benzylidene-3-cyano-4-phenyl-6,7-dihydro-1*H*-cyclopenta[*b*]pyridin-2(5*H*)-one **5a**. The structure of **4a** was determined by ^1H NMR spectroscopy. This compound produced four doublets at δ 5.02 (0.5 H, $J=7.5$ Hz), 4.77 (0.5 H, $J=12.6$ Hz), 4.36 (0.5 H, $J=12.6$ Hz) and 4.13 (0.5 H, $J=7.5$ Hz), which indicates that there are two protons at 3- and 4-position of this 2-pyridone. According to the literature [2–7], the relevant multistep reactions all afforded **5a** as a major product under basic conditions. Consequently, the use of YbCl_3 as a Lewis acid-type catalyst in the present reaction can be considered a key factor affecting the structure of product, and the reaction mechanism may be different in acidic and basic conditions.

The following reaction conditions for the model reaction were then investigated: catalyst loading, reaction time, reaction temperature, and solvent. The results are listed in Table 1. When the catalyst loading was increased from 5 mol% to 20 mol% the yield increased considerably, but the further increase in the catalyst loading did not improve the yield. Among the solvents screened, ethanol gave the best result. Several lanthanide chlorides were tested to assess the influence of the central metal on the catalytic activity. The order of catalytic activity was $\text{Yb} > \text{Y} \approx \text{Er} > \text{La}$, which is the reverse order to the ionic radii of these lanthanides. Thus, YbCl_3 was chosen as the representative lanthanide catalyst

and the optimum reaction conditions were established for subsequent experiments. In a typical experimental procedure, **1a** (2 mmol), **2a** (3 mmol) and YbCl_3 (0.3 mmol) were mixed and heated at 120°C for 6 h. Then **3** (2 mmol) and ethanol (4 mL) were added. The resulting mixture was refluxed for 24 h. The yellow precipitate was filtered and washed with EtOH and water to afford the target product **4a**.

To examine the scope and generality of this method, the process was extended to various aromatic aldehydes and cyclic ketones under the optimum reaction conditions (Scheme 3). As summarized in Table 2, the method was equally effective for five-membered and six-membered cyclic ketones and all the reactions proceeded smoothly affording the desired arylidene heterobicyclic 3-cyano-2-pyridones in moderate to good yields. The reaction could also be used for aromatic aldehydes with *ortho*-, *meta*- and *para*-substituents, and tolerated both electron deficient and rich aldehydes.

A byproduct was isolated from the crude product of our model reaction, which was characterized as α,α' -dibenzylidene cyclopentanone **C** and should be produced from benzaldehyde and cyclopentanone. This finding directed us to a plausible mechanism. It can be suggested that the first step of the present reaction is probably a Lewis acid-catalyzed cross-aldol condensation of aldehyde with ketone to produce **C**, which is similar to the $\text{Yb}(\text{OTf})_3$ catalyzed reaction described by Wang et al. [17]. The Michael addition of cyanoacetamide to **C** leads to **D**, which subsequently eliminates water and cyclizes to form the product (Scheme 4). To confirm this mechanism, a supplementary experiment was carried out using α,α' -dibenzylidene cyclopentanone **C** as the substrate. **C** was mixed with cyanoacetamide and YbCl_3 (20 mol%) and the resulting mixture was stirred in EtOH under reflux for 70 h. After work up, product **4a** was obtained in 75% yield, indicating that **C** was the key intermediate in this tandem condensation process.

In conclusion, an efficient route was developed for the

Scheme 2

Scheme 3

Table 1 Screening of reaction conditions for the tandem condensation of cyclopentanone, benzaldehyde and cyanoacetamide^{a)}

Entry	Catalyst	Loading (mol%)	Temperature (T_1/T_2) ^{b)} (°C)	Solvent	Time (t_1+t_2) ^{c)} (h)	Yield (%)
1	YbCl ₃	5	120/90	EtOH	6+24	17
2	YbCl ₃	10	120/90	EtOH	6+24	42
3	YbCl ₃	15	120/90	EtOH	6+24	62
4	YbCl ₃	20	120/90	EtOH	6+24	75
5	YbCl ₃	25	120/90	EtOH	6+24	75
6	YbCl ₃	20	100/90	EtOH	6+24	68
7	YbCl ₃	20	120/90	EtOH	2+24	57
8	YbCl ₃	20	120/90	EtOH	6+70	79
9	YbCl ₃	20	120/70	THF	6+24	5
10	YbCl ₃	20	120/120	DMF	6+24	8
11	YbCl ₃	20	120/90	Toluene	6+24	44
12	LaCl ₃	20	120/90	EtOH	6+24	37
13	ErCl ₃	20	120/90	EtOH	6+24	62
14	YCl ₃	20	120/90	EtOH	6+24	64

a) Reaction conditions: **1a**, **2a** and catalyst were mixed and heated at temperature T_1 (°C) for time t_1 (h). Then **3** and solvent were added and the resulting mixture was heated at temperature T_2 (°C) for time t_2 (h). b) The first temperature is for T_1 and the second temperature is for T_2 . c) The first time is for t_1 and the second time is for t_2 .

Table 2 YbCl₃-catalyzed condensation of cyclic ketones, aromatic aldehydes and cyanoacetamide^{a)}

Entry	Cyclic ketone	Ar	Product	Yield (%)
1		Ph	4a	75
2		4-ClPh	4b	80
3		3-CH ₃ OPh	4c	82
4		3-FPh	4d	77
5		2-CH ₃ Ph	4e	76
6		2-ClPh	4f	62
7		Ph	4g	65
8		4-CH ₃ OPh	4h	63
9		4-CH ₃ Ph	4i	74
10		4-BrPh	4j	78
11		4-FPh	4k	70
12		3-FPh	4l	70
13		4-CH ₃ OPh	4m	65
14		4-ClPh	4n	77
15		4-BrPh	4o	88

a) Reaction conditions: **1**:**2**:**3** = 0.67:1:0.67, 10 mol% YbCl₃ relative to aromatic aldehyde. **1**, **2** and YbCl₃ were mixed and heated at 120°C for 6 h. Then **3** and EtOH were added and the resulting mixture was refluxed for 24 h.

Scheme 4

synthesis of arylidene heterobicyclic 3-cyano-2-pyridones via tandem condensation of aromatic aldehydes, cyclic ketones, and cyanoacetamide with YbCl_3 as a catalyst. This reaction is atom-economic and can be performed easily. Further applications of this tandem method to the synthesis of biologically active azaheterocyclic compounds are in progress in our laboratory.

This work was supported by the National Natural Science Foundation of China (20872106, 20972107).

- 1 Robertson D W, Beedle E E, Swartzendruber J K, et al. *J Med Chem*, 1986, 29: 635–640
- 2 El-Subbagh H I, Abu-Zaid S M, Mahran M A, et al. *J Med Chem*, 2000, 43: 2915–2921
- 3 Koji S, Satoshi K, Akio S, et al. *Synthesis*, 1981, 211–213

- 4 Shestopalov A M, Sharanin Y A. *Zhurnal Organicheskoi Khimii*, 1986, 22: 1291–1297
- 5 Shestopalov A M, Sharanin Y A. *Zhurnal Organicheskoi Khimii*, 1986, 22: 1163–1168
- 6 Otto H H. *Monatsh Chem*, 1978, 109: 681–693
- 7 Jain R, Roschangar F, Ciufolini M A. *Tetrahedron Lett*, 1995, 36: 3307–3310
- 8 Molander G A, Romero J A C. *Chem Rev*, 2002, 102: 2161–2185
- 9 Kobayashi S, Sugiura M, Kitagawa H, et al. *Chem Rev*, 2002, 102: 2227–2302
- 10 Hong S, Marks T J. *Acc Chem Res*, 2004, 37: 673–686
- 11 Shibasaki M, Matsunaga S. *Chem Soc Rev*, 2006, 35: 269–279
- 12 Han X Y, Xu F, Luo Y Q, et al. *Eur J Org Chem*, 2005, 1500–1503
- 13 Zhou Z Q, Xu F, Han X Y, et al. *Eur J Org Chem*, 2007, 5265–5269
- 14 Zhang H H, Zhou Z Q, Yao Z G, et al. *Tetrahedron Lett*, 2009, 50: 1622–1624
- 15 Ji X F, Cai L J, Yao Z G, et al. *Heteroatom Chem*, 2010, 21: 89–95
- 16 Yao L B, Xu F, Qi S. *Chin Sci Bull*, 2010, 55: 4108–4111
- 17 Wang L, Sheng J, Tian H, et al. *Synthesis*, 2004, 3060–3064

Open Access This article is distributed under the terms of the Creative Commons Attribution License which permits any use, distribution, and reproduction in any medium, provided the original author(s) and source are credited.